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Does morphine remain a standard of care in acute myocardial infarction?

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ABSTRACT

Morphine is routinely used for pain relief in patients with acute myocardial infarction. However, it was documented that morphine decreases the bioavailability and antiplatelet effect of $P2Y_{12}$ receptor inhibitors. Multiple strategies to overcome this undesirable interaction are currently under investigation; they include the following: administration of crushed ticagrelor tablets, co-administration of metoclopramide, bridging with intravenous antiplatelet agents, or replacement of morphine with other analgesic. Adequately powered randomised trials examining the clinical consequences of concomitant use of morphine and $P2Y_{12}$ receptor inhibitors are still lacking.

Key words: morphine, $P2Y_{12}$ receptor inhibitors, clopidogrel, ticagrelor, prasugrel, myocardial infarction

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Introduction

Alleviation of chest pain is of paramount importance in the treatment of patients with acute myocardial infarction (MI). Titrated intravenous morphine is the most widely used method in this clinical setting [1]. The choice of such powerful analgesics as opioids is motivated by the necessity of providing comfort, but also to attenuate sympathetic activation, which leads to vasoconstriction and increased afterload of the heart. According to the current European Society of Cardiology (ESC) guidelines on acute myocardial infarction in patients presenting with ST-segment elevation (STEMI), titrated intravenous opioids should be considered to relieve pain (class of recommendation IIa, level of evidence C) [2]. It is noteworthy that, as compared to previous guidelines, the class of recommendation for morphine use in STEMI has been lowered from I to IIa (i.e. from "it is indicated" to "it should be considered") with the same level of evidence C (i.e. consensus of opinion of the experts) due to the unfavourable impact of morphine on $P2Y_{12}$ inhibitors bioavailability and antiplatelet effect [2–4].

Interaction between morphine and antiplatelet agents

Dual antiplatelet therapy composed of aspirin and a $P2Y_{12}$ receptor inhibitor is a cornerstone of treatment in patients with acute coronary syndromes (ACS) [4, 5]. In modern ACS therapy the ESC guidelines clearly recommend the use of more potent antiplatelet agents like ticagrelor and prasugrel over clopidogrel [6]. In a double-blind cross-over trial in healthy volunteers, morphine had no significant effect on aspirin-induced platelet inhibition [7]. The first reports suggesting possible drug-drug interaction between morphine and clopidogrel come from the CRUSADE registry [8]. In this registry the incidence of the composite endpoint of death and myocardial infarction was significantly higher in patients who received intravenous morphine as compared with those who did not. In a randomised, placebo-controlled, pharmacokinetic trial in healthy volunteers the administration of morphine was associated with delayed and reduced maximal plasma concentration of ticagrelor [9]. In the first hours of treatment in STEMI, as compared with non-ST-segment elevation

myocardial infarction (NSTEMI), ticagrelor concentrations as well as its antiplatelet effect was found to be reduced in the prospective, observational PINPOINT trial [10]. It was further documented that independent predictors of high on-treatment platelet reactivity within the initial hours of antiplatelet treatment with ticagrelor in ACS patients are the presence of STEMI and morphine co-administration [11]. The first randomised study demonstrating the unfavourable interaction between morphine and ticagrelor in the acute MI setting was the double-blind, placebo-controlled, pharmacokinetic-pharmacodynamic IMPRESSION trial [4]. The study provided evidence that morphine decreases not only the bioavailability, but also the antiplatelet effect of ticagrelor in patients with MI. Similar observations of delayed onset of action with concomitant use of morphine were also reported for prasugrel [12, 13].

The mechanism of interaction between morphine and $P2Y_{12}$ receptor inhibitors

Morphine frequently induces nausea and vomiting [14]. Moreover, the stimulation of opioid receptors in the myenteric plexus and the intestines is responsible for reduction of intestinal motility and production of intestinal secretes [15]. Additionally, increased sympathetic activation and selective perfusion of vital organs results in delayed stomach emptying, slower intestinal transit, and deferred drug absorption. Interestingly, impaired gastrointestinal absorption is probably also responsible for the delayed antiplatelet effect of potent $P2Y_{12}$ inhibitors observed within the first hours of treatment in MI patients managed with mild therapeutic hypothermia, as well as in critically ill patients [16, 17].

Therapeutic strategies to overcome the interaction between morphine and $P2Y_{12}$ receptor inhibitors

Several options have been proposed in the literature to either avoid or diminish the undesirable interaction between morphine and $P2Y_{12}$ receptor inhibitors. First, administration of crushed ticagrelor tablets as compared with the integral ones was associated with shorter time to reach maximum plasma concentration of ticagrelor and lower platelet reactivity at one hour post loading dose in STEMI patients [18]. It is worth mentioning that sublingual administration of crushed ticagrelor tablets was related to slower absorption and higher platelet reactivity within the first hour following ticagrelor loading dose, compared with crushed tablets administered orally in patients with unstable angina [19]. Second, the co-administration of a prokinetic agent — metoclopramide — was associated with higher ticagrelor concentration and lower platelet reactivity within the first hour post ticagrelor loading dose in patients with unstable angina [20]. Third, the idea of intravenous co-administration of a peripheral opioid antagonist — methylnaltrexone — showed only marginal differences in ticagrelor concentration and no effect on platelet reactivity [21]. Fourth, the co-administration of a glycoprotein IIb/IIIa receptor antagonist — abciximab — provided prompt and efficient platelet inhibition in prasugrel-treated STEMI patients receiving morphine [13]. Fifth, although it has not been examined yet, the co-administration of an intravenous direct-acting $P2Y_{12}$ receptor antagonist — cangrelor — might also be a possible solution [22]. And, sixth, the last proposed strategy to overcome the negative impact of morphine may be a replacement of morphine with another powerful, short-acting opioid analgesic like alfentanil [23].

Clinical consequences of interaction between morphine and $P2Y_{12}$ receptor inhibitors

Morphine co-administration in ticagrelor-treated patients with ACS is a strong predictor of high on-treatment platelet reactivity within the first hours after ticagrelor loading dose, when a sufficient antiplatelet effect is particularly desired [11]. High on-treatment platelet reactivity is a significant and well-documented risk factor of atherothrombotic events [24–26]. It has been postulated that delayed onset of antiplatelet action in MI patients receiving morphine may translate into increased risk of adverse cardiovascular events [4, 9, 27–29]. However, to date, we lack adequately powered randomised studies investigating this hypothesis. Additionally, morphine use in STEMI patients is not only associated with increased platelet reactivity, but also reduced spontaneous myocardial reperfusion and larger infarct size [30]. In a recently published meta-analysis including one randomised trial and 10 observational studies, periprocedural intravenous morphine use in STEMI patients treated with an oral $P2Y_{12}$ receptor inhibitor (ticagrelor 59.7%, clopidogrel 33.5%, and prasugrel 6.8%) and undergoing PCI was not associated with adverse short-term clinical outcomes [31]. Yet, the included randomised trial comprised only 35 morphine-treated subjects, and there was only one reported adverse event [4]. Further randomised trials exploring the effect of morphine use on clinical outcomes in MI patients are greatly needed.

Conclusions

I. Morphine decreases bioavailability and antiplatelet effect of $P2Y_{12}$ receptor inhibitors in patients with acute MI.
II. Therapeutic strategies to overcome the interaction between morphine and $P2Y_{12}$ receptor inhibitors include: administration of crushed ticagrelor tablets, co-administration of metoclopramide, bridging with abciximab or cangrelor, or replacement of morphine with short-acting alfentanil.
III. Adequately powered randomised studies exploring the influence of concomitant use of morphine and $P2Y_{12}$ receptor inhibitors on clinical outcomes are lacking.
IV. Morphine remains a standard of care in acute MI; however, it should be co-administered with antiplatelet agents after careful evaluation of the clinical situation.

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